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ORIGINAL PAPER

Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus i.v. bolus fluorouracil/ leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology study 0401

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Abstract
Purpose Oxaliplatin combined with either fluorouracil/ leucovorin (OXAFAFU) or capecitabine (OXXEL) has a demonstrated activity in metastatic colorectal cancer patients. We aimed at comparing these two regimens in terms of response rate (RR), safety, progression-free survival (PFS), and quality of life (QoL) of patients.
Methods A total of 322 patients with metastatic colorectal cancer were randomized to receive biweekly: oxaliplatin 100 mg/m^2 i.v. on day 1, capecitabine 1,000 mg/m^2 orally twice daily from day 1 to day 11 (OXXEL); or oxaliplatin 85 mg/m^2 i.v. on day 1; 6S-leucovorin 250 mg/m^2 i.v. and fluorouracil 850 mg/m^2 i.v. on day 2 (OXAFAFU).
Results Eleven complete and 42 partial responses were registered with OXXEL (RR = 34%); six complete and 48 partial responses were obtained with OXAFAFU (RR = 33%) ($P = 0.999$). Severe adverse events were less frequent (32 vs. 43%) with OXXEL, which also reduced the occurrence of severe neutropenia (10 vs. 27%) and febrile neutropenia (6 vs. 13%), but produced more gastric side effects (8 vs. 3%) and diarrhea (13 vs. 8%). QoL did not differ across the two arms. Median PFS was 6.6 months in the OXXEL, and 6.5 months in the OXAFAFU arm (HR = 1.12, $P = 0.354$). Median overall survival was 16.0 and 17.1 months (HR = 1.01, $P = 0.883$).
Conclusions OXXEL and OXAFAFU regimens were equally active in metastatic colorectal cancer. The choice should be based on patient preference and on pharmacoeconomic evaluations.

Keywords Capecitabine · Oxaliplatin · OXXEL regimen · OXAFAFU regimen · Colorectal carcinoma · Randomized trial

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Introduction

Oxaliplatin as a single agent has demonstrated activity in both chemonaive and fluorouracil-pretreated colorectal cancer patients (Raymond et al. 1998; Becouarn et al. 1998; Díaz-Rubio et al. 1998; Machover et al. 1996). Moreover, in vitro studies on colon cancer cell lines have shown a synergism between oxaliplatin and fluorouracil, which was greater when oxaliplatin preceded a short fluorouracil exposure (Fischel et al. 1998).

In randomized clinical trials, oxaliplatin combined with fluorouracil and leucovorin produced a greater response rate and a longer time to progression than fluorouracil and leucovorin alone; however, median survival times were similar (Giacchetti et al. 2000; de Gramont et al. 2000). Thereafter, the FOLFOX4 regimen has been demonstrated to be significantly more effective in terms of response rate, time to progression, and overall survival than the irinotecan plus leucovorin/fluorouracil (IFL) i.v. bolus regimen (Goldberg et al. 2004). This observation was confirmed in a subsequent randomized trial comparing FOLFOX4 with a modified IFL regimen (Goldberg et al. 2006). Moreover, the SICOG trial 9801 compared oxaliplatin and irinotecan in combination with leucovorin-modulated fluorouracil i.v. bolus every 2 weeks. The OXAFAFU regimen produced a significantly greater response rate, and a significantly longer progression-free and overall survival than the IRIFAFU regimen, with a less pronounced toxicity (Comella et al. 2005).

More recently, the combination of oxaliplatin and capecitabine has been investigated in several multicentre phase II/III studies in metastatic colorectal cancer. The XELOX regimen (oxaliplatin 130 mg/m^2 i.v. on day 1, and capecitabine 2,000 mg/m^2 orally days 1–14, every 3 weeks) achieved a 55% response rate, and a 19.5 months median overall survival in a large multicentre international phase II trial (Cassidy et al. 2004). A similar combination, with oxaliplatin 120 mg/m^2 on day 1 and capecitabine 2,500 mg/m^2 days 1–14, obtained a 44% response rate, and a median survival time of 20 months; however, occurrence of grade $\geq$3 diarrhea was seen in 28% of patients (Zeuli et al. 2003). Furthermore, a phase II randomized study assessed the addition of oxaliplatin 70 mg/m^2 (CAPOX) or irinotecan 80 mg/m^2 (CAPIRI) on days 1 and 8 to capecitabine 2,000 mg/m^2 given for 2 weeks, reporting a 50.7% response rate with the CAPOX regimen (Grothey et al. 2003). In a Swiss phase II study, 26 pretreated and 43 chemonaive patients received oxaliplatin 130 mg/m^2 and capecitabine 2,500 mg/m^2 on day 1–14 every 3 weeks. A response rate of 49%, and a median overall survival time of 17.1 months were reported in previously untreated patients (Borner et al. 2002). The feasibility and activity of the XELOX regimen in elderly patients has also been investigated: a 37% response rate, with 8.5 months of median progression-free survival and 14.4 months of median survival, have been reported (Comella et al. 2005). These findings were subsequently confirmed by Feliu et al. (2006), who reported a 36% response rate, a median progression-free survival of 5.8 months, and an overall survival of 13.2 months.

Recently, we have assessed a different schedule of this combination, including oxaliplatin 100 mg/m^2 on day 1, and capecitabine 1,000 mg/m^2 bid from day 1 (evening) to day 11 (morning), recycling every 2 weeks (OXXEL regimen). The rationale was to keep the same dose intensity for capecitabine as in the 3-weekly regimen, while slightly increasing the dose intensity of oxaliplatin. We achieved with this treatment a 45% response rate, and a median progression-free survival of 7.9 months; occurrence of severe side effects was negligible (Comella et al. 2005).

Based on these premises, we devised to conduct a randomized trial to compare the OXXEL and OXAFAFU regimens in metastatic colorectal cancer patients. Preliminary comparative data on the safety have already been reported (Sandomenico et al. 2006). Here we present the final results in terms of efficacy and quality of life of treated patients.

Methods

Patient selection

This trial was approved by the Independent Ethics Committee of the National Tumor Institute of Naples, and all participating patients provided a written informed consent. Eligible patients had histologically proven diagnosis of advanced adenocarcinoma of the colon or rectum, age $\geq$18 years, life expectancy >3 months, and ECOG performance status $\leq$2. Additional inclusion criteria were: adjuvant chemotherapy completed at least 6 months before, presence of a bidimensionally measurable lesion, neutrophil count $\geq 2 \times 10^6$/L, platelet count $\geq 100 \times 10^6$/L, hemoglobin level $\geq$100 g/L, serum bilirubin $\leq$1.25 times the upper normal limit (UNL), serum alanine aminotransferase and aspartate aminotransferase $\leq 2.5 \times$ UNL in absence of liver metastasis, or $\leq 5 \times$ NL in presence of liver metastasis; normal renal function.

Patients evaluation

Biochemistry profile, blood cell count with white blood cell (WBC) count and differential, and carcinoembryonic antigen (CEA) serum level assessment, were performed at baseline. Target lesions were measured by computed tomography (CT) or magnetic resonance imaging (MRI) scans not more than 4 weeks before initial therapy. During

treatment, WBC count with differential was performed weekly. Biochemistry, symptoms, body weight, and non-hematological toxicity were checked before each cycle. Toxicity was scored according to WHO criteria (Miller et al. 1981), while neuropathy was defined according to the Lévi scale (Lévi et al. 1992), and the worst toxicity suffered by each patient during the whole treatment was recorded.

Patients were required to fulfill the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30 version 3.0) before randomization, and every 8 weeks during treatment. Changes >10 points of the baseline scores were considered clinically meaningful (Osoba et al. 1998).

CT or MRI scan was repeated after every 4 cycles, and at the end of treatment. Response was defined according to WHO criteria (Miller et al. 1981), and reassessed 8 weeks after the date of their first documentation; only confirmed responses were computed in the activity analysis.

Treatment

Patients, after stratification according centre, performance status, and previous exposure to adjuvant chemotherapy, were randomly allocated to receive: oxaliplatin 100 mg/m^2 i.v. (2 h) on day 1; capecitabine 1,000 mg/m^2 orally twice daily (12-h apart) from day 1 (evening) to day 11 (morning) (OXXEL regimen); or oxaliplatin 85 mg/m^2 i.v. (2 h) on day 1; 6S-leucovorin 250 mg/m^2 i.v. (2 h), followed by fluorouracil 850 mg/m^2 i.v. bolus on day 2 (OXAFAFU regimen). In both arms, cycles were repeated every 2 weeks, until progression, unacceptable toxicity or patient refusal, or for a maximum of 12 cycles.

After discontinuation of first-line treatment, patients were followed every 2 months to assess the disease status and survival. Further treatment was not planned, and it was left to the single investigator choice.

Statistical considerations and analysis

Primary end-point of this study was to compare the activity of the two regimens. Since a great difference was unlikely on the ground of our previous trials, we planned to have an 80% power to demonstrate, with an alpha error = 0.05, a 15% minimum difference in response rate between the two arms. The planned accrual was 150 patients per arm. This sample size also allowed to make a comparison of progression-free survival. Indeed, 257 events had a 90% power to demonstrate, with an alpha error = 0.05, a 33% reduction of the hazard of progression. The predefined target population had also an 80% power to demonstrate (with alpha error = 0.05) a 20% difference in the proportion of patients showing a QoL preservation (i.e., $a < 10$-point decrease from the baseline score) after 8 weeks from initial therapy.

Frequencies were calculated with their 95% confidence limits (CL), and compared with the chi-squared or Fisher's exact test. A logistic regression analysis was performed to ascertain the independent effect on response of some baseline patient characteristics: sex, primary site, previous surgery, previous adjuvant chemotherapy, previous loss >5% of body weight, performance status, abnormal CEA serum level, presence of synchronous metastases, presence of liver metastases, or metastases confined to liver were included as dichotomous variables, while age, tumor grading, serum alkaline phosphatase concentration, and number of disease sites were included as continuous variables. Time-to event probabilities were estimated with the Kaplan and Meier method (Kaplan and Meier 1958), and compared with the two-sided log-rank test (Mantel 1966). Baseline demographic and clinical characteristics were included in a Cox multivariate analysis (Cox 1972) to assess their independent effect on failure-free, progression-free, and overall survival.

Results

From May 2004 to April 2007, 344 patients were registered into this study. However, 12 patients did not met all the inclusion criteria, leaving 322 eligible patients, who were randomized to the OXXEL (158 patients) or OXAFAFU (164 patients) arm. Baseline characteristics were usually well balanced between the two arms of treatment. However, there were more males and more patients with liver only metastases in the OXXEL arm. Conversely, more patients in the OXAFAFU arm had an elevated CEA basal value (Table 1).

Delivered treatment and toxicity

A total of 1,251 cycles of OXXEL, and 1,282 cycles of OXAFAFU were delivered, with a median number of eight (range 1–12) cycles/patient in both arms. Comparable proportions of patients in the two arms received 4, 8 or 12 cycles (Table 2). Median duration of treatment was 17 (range 1–36) weeks in either arm.

Median cumulative oxaliplatin dose was significantly greater ($P = 0.001$) for patients treated with OXXEL (739 mg/m^2, range 75–1,232 mg/m^2) than with OXAFAFU (659 mg/m^2, range 63–1,069 mg/m^2). Similarly, median dose intensity of oxaliplatin was higher for the former (43 mg/m^2 per week, range 14–81 mg/m^2 per week) than for the latter (34 mg/m^2 per week, range, 13–78 mg/m^2 per week) ($P = 0.001$). Median relative dose intensities of this drug were similar in the two arms (84 vs. 80%).

Table 1 Demographic and clinical characteristic according to arms of treatment

Arm characteristics	OXAFAFU		Fisher's test	OXXEL		Total	
	No.	%		No.	%	No.	%
Eligible patients	164	100		158	100	322	100
Males	89	54	0.023	104	66	193	58
Females	75	46		54	34	129	42
Median age (range)	65 (37–79)			64 (39–84)		63 (37–84)	
Aged ≥70 years	65	40		51	32	116	36
Primary tumor							
Colon	115	76		114	72	229	71
Rectum	49	24		44	28	93	29
Grading							
Well differentiated	14	9		10	6	24	7
Moderately differentiated	92	56		103	65	195	61
Poorly differentiated	31	19		29	18	60	19
Unknown	27	16		16	10	43	13
Previous surgery	125	76		114	72	239	74
Previous adjuvant chemotherapy	41	25		39	25	80	25
ECOG Performance Status							
0	99	60		96	61	195	61
1	59	36		57	36	116	36
2	6	4		5	3	87	3
No. disease sites							
1	74	45		79	50	153	48
2	55	33		45	29	100	31
3+	35	21		34	21	69	21
Liver positive	123	75		131	83	254	79
Liver only	48	29	0.023	64	41	112	35
Synchronous metastasis	96	59		91	58	124	58
Weigh loss ≥5%	40	24		44	28	84	26
Alkaline phosphatase > UNL	59	36		53	34	112	35
CEA value							
>5 ng/mL	143	87	0.007	120	76	263	82
>100 U/mL	40	24		33	21	73	23

In the OXXEL arm, median dose intensity for capecitabine was 8,046 (range 5,450–12,000) mg/m^2 per week (80% of the planned one); in the OXAFAFU arm, median dose intensity of fluorouracil was 308 (range 153–406) mg/m^2 per week (72% of the intended one).

Occurrence of severe neutropenia (10 vs. 27%, $P < 0.001$) and febrile neutropenia (6 vs. 13%, $P = 0.043$) was significantly lower with the OXXEL treatment, while frequencies of grade ≥3 thrombocytopenia (4 vs. 3%) and anemia (3 vs. 1%) were similar. Severe diarrhea affected more patients treated with OXXEL (13 vs. 8%), but this difference was not significant. However, gastric intolerance was more common with the oral assumption of capecitabine (8 vs. 3%, $P = 0.028$). Other non-hematological side effects were registered in few patients, and were comparable in both arms (Table 3). Despite the greater amount of oxaliplatin delivered with OXXEL, this treatment did not produce more severe neuropathy than OXAFAFU regimen (10 vs. 7%). On the whole, treatment-related severe adverse events affected significantly less patients in OXXEL than in OXAFAFU arm (32 vs. 43%, $P = 0.026$). Early deaths (within 60 days from initial therapy) were registered in similar proportions in both arms (3 vs. 4%). In OXXEL arm, a toxic death was caused by severe diarrhea and dehydration in two elderly patients. These patients had previously received several cycles of chemotherapy without experiencing severe toxicity, and had a normal renal function.

Activity

Eleven complete and 42 partial responses were registered in the OXXEL arm, for a response rate of 34%; six complete and

Table 2 Treatment disposition in the two arms of treatment

Arm characteristics	OXAFAFU		Fisher's test	OXXEL		Total	
	No.	%		No.	%	No.	%
Eligible patients	164	100		158	100	322	100
Total number of cycles	1,272			1,243		2,515	
Median cycles/patient (range)	8	1–12		8	1–12	8	1–12
Patients treated with:							
≥4 cycles	146	89		141	89	287	89
≥8 cycles	97	59		96	61	193	60
≥12 cycles	46	28		45	28	91	28
Patients still on therapy	7	4		7	4	14	4
Patients off treatment for:							
Protocol	110	67		101	64	210	65
Refusal	13	8		16	10	29	9
Toxicity	10	6	0.015	21	13	32	10
Disease complications	14	8		5	3	19	6
Physician's decision	10	6		8	5	18	5

Table 3 Frequencies of main side effects according to arms of treatment

Arm	OXAFAFU		OXXEL		Fisher's test	
WHO toxicity (%)	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Neutropenia	49	27	15	10	0.001	0.001
Febrile neutropenia	–	13	–	6	–	0.043
Anemia	30	1	23	3	ns	ns
Thrombocytopenia	21	3	24	4	ns	ns
Diarrhea	43	8	36	13	ns	ns
Neuropathy	43	7	48	10	ns	ns
Gastric symptoms	41	3	50	8	ns	0.028
Stomatitis	18	2	15	2	ns	ns
Liver toxicity	15	1	22	0	ns	ns
Hair loss	14	0	7	0.6	ns	ns
Hand & foot syndrome	10	1	15	4	ns	ns
Renal toxicity	4	0.6	8	2	ns	ns
Allergic reactions	4	3	3	0.6	ns	ns
Fatigue	4	1	5	1	ns	ns

ns not significant

48 partial responses were registered in the OXAFAFU arm, for a response rate of 33% (odds ratio = 1.03, 95% CL, 0.63–1.68, $P = 0.999$). An overall disease control (response or stabilization) was achieved in 68 and 70% patients, respectively.

Regardless of received treatment, response rate was slightly higher in patients with synchronous metastases (37 vs. 27%), and in younger (≤60-year-old) patients (40 vs. 30%). At the multivariate analysis, only age of patients (as continuous variable) adversely affected the probability of response ($P < 0.001$).

Median failure-free survival was 4.9 (95% CL, 4.2–5.6) months for patients treated with OXXEL, and 4.7 (95% CL, 4.0–5.4) months for patients treated with OXAFAFU (hazard ratio [HR] = 0.92, 95% CL, 0.73–1.17; $P = 0.555$). At Cox analysis, only the number of disease sites was significantly associated with a shorter failure-free survival ($P = 0.049$).

Median progression-free survival was 6.6 (95% CL, 6.0–7.0) for patients treated with OXXEL, and 6.5 (95% CL, 5.4–7.6) months for those treated with OXAFAFU (HR = 1.12, 95% CL, 0.88–1.45, $P = 0.354$) (Fig. 1). Number of disease sites ($P = 0.001$), followed by an elevated basal CEA value ($P = 0.036$) were negative factors for progression-free survival.

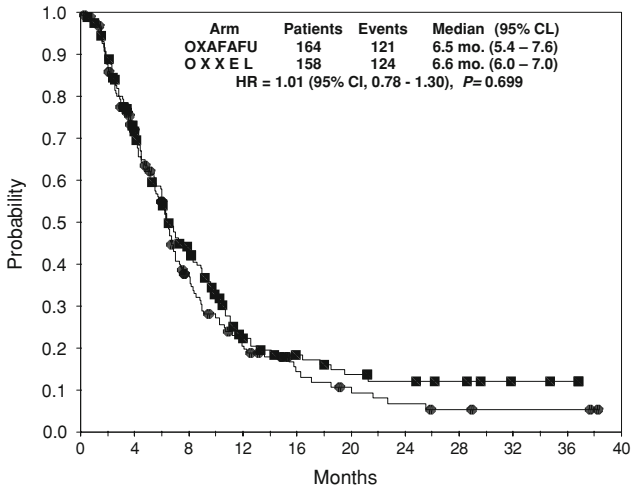

Fig. 1 Estimated progression-free survival curves according to arms of treatment (OXAFAFU *squares*, OXXEL *circles*)

Quality of life evaluation

Three-hundred and twelve (97%) eligible patients (OXXEL arm, 151 patients; OXAFAFU arm, 161 patients) filled in the baseline questionnaire. After 8 weeks, the questionnaire was available for 225 of 287 (78%) patients on therapy. After 16 weeks, 193 patients were on therapy, and questionnaires were available for 156 (81%) patients. Finally, after 24 weeks, the available questionnaires were 72 (79%) of 91 patients still on therapy.

Baseline single item and global health status/quality of life scores did not significantly differ between the two arms. Excluding constipation ($P = 0.001$) and financial item score ($P = 0.004$), no other significant differences in the change of single scores were observed between the two arms during the whole treatment (Table 4).

At the predetermined time-point for the comparison, a preservation of the quality of life was reported in 47% of patients in either arm. After 16 weeks, a higher proportion of patients in the OXXEL than in OXAFAFU arm showed a deterioration of the global health status/quality of life score; the same trend was also observed after 24 weeks. However, these differences were not statistically significant (Table 5).

Overall survival

As of October 2007, after a median follow-up of 24 (range 6–42) months, 162 (50%) patients have died (78 patients in the OXXEL, and 84 patients in the OXAFAFU arm). Median overall survival was 16.0 (95% CL, 11.2–20.2) months, and 17.1 (95% CL, 13.8–20.4) months, respectively (HR = 1.01, 95% CL, 0.74–1.38, $P = 0.883$). One-, 2- and 3-year probabilities of survival were 59, 36 and 31% for the OXXEL arm, and 63, 35 and 26% for the OXAFAFU arm (Fig. 2).

Table 4 Quality of life of patients according to arms of treatment (values are means and standard errors)

	Baseline assessment		After 8 weeks		After 16 weeks		After 24 weeks	
	OXXEL	OXAFAFU	OXXEL	OXAFAFU	OXXEL	OXAFAFU	OXXEL	OXAFAFU
	151[a]	161[a]	107[a]	118[a]	83[a]	73[a]	33[a]	39[a]
Items								
Physical	81 (1.4)	80 (1.5)	79 (2.1)	75 (1.8)	80 (2.1)	74 (2.6)	83 (4.6)	74 (2.6)
Role	76 (2.4)	75 (2.1)	76 (2.7)	68 (3.4)	79 (2.5)	76 (3.6)	77 (5.7)	85 (3.6)
Emotional	72 (1.7)	68 (1.7)	70 (2.2)	71 (2.1)	74 (2.1)	72 (2.9)	72 (3.8)	75 (3.7)
Cognitive	87 (1.7)	85 (1.5)	82 (2.7)	83 (1.8)	85 (2.3)	82 (3.0)	86 (4.2)	77 (9.0)
Social	82 (1.8)	80 (2.1)	78 (2.5)	77 (2.1)	77 (2.9)	79 (3.1)	78 (5.2)	87 (3.1)
Fatigue	28 (1.9)	30 (1.9)	31 (2.5)	37 (2.4)	30 (2.2)	38 (3.9)	34 (5.1)	28 (3.6)
Nausea/Vomiting	5 (0.9)	6 (1.3)	15 (2.3)	13 (1.6)	12 (1.7)	12 (2.4)	10 (3.8)	4 (1.5)
Pain	18 (1.9)	13 (1.5)	23 (4.1)	21 (2.2)	15 (2.5)	16 (2.9)	23 (4.8)	13 (2.9)
Dyspnoea	9 (1.4)	13 (1.6)	12 (2.3)	14 (1.6)	11 (2.2)	12 (2.5)	19 (4.7)	9 (2.9)
Insomnia	25 (2.3)	31 (2.4)	26 (2.9)	24 (2.4)	20 (2.8)	23 (3.3)	29 (5.5)	16 (3.7)
Appetite loss	16 (2.1)	18 (1.9)	23 (2.1)	21 (1.9)	19 (2.9)	22 (3.4)	16 (4.5)	11 (3.1)
Constipation	20 (2.4)	20 (2.1)	16 (2.6)	22 (2.7)	13 (2.6)	27 (3.5)	10 (3.2)	15 (3.4)
Diarrhoea	9 (1.5)	10 (1.5)	16 (2.4)	20 (2.5)	14 (2.2)	15 (2.8)	10 (3.6)	11 (3.3)
Financial difficulties	17 (2.2)	20 (2.1)	19 (2.8)	18 (1.8)	19 (3.0)	21 (3.9)	25 (5.5)	19 (2.9)
General health status	66 (1.8)	65 (1.7)	65 (2.2)	65 (1.8)	70 (2.2)	67 (2.5)	67 (5.1)	69 (2.9)

[a] Number of patients assessed

Table 5 Patients showing a significant change of the quality of life score during treatment: improved means a ≥10 points increment of the baseline score; deteriorated means a ≥10-point decrease of the baseline score

Arm	After 8 weeks			After 16 weeks			After 24 weeks		
	Improved	Stable	Deteriorated	Improved	Stable	Deteriorated	Improved	Stable	Deteriorated
OXXEL	24 (23%)	50 (47%)	30 (30%)	30 (37%)	29 (35%)	23 (28%)	5 (17%)	2 (7%)	47 (76%)
OXAFAFU	25 (22%)	56 (47%)	37 (31%)	17 (24%)	40 (57%)	13 (19%)	1 (3%)	7 (18%)	30 (79%)

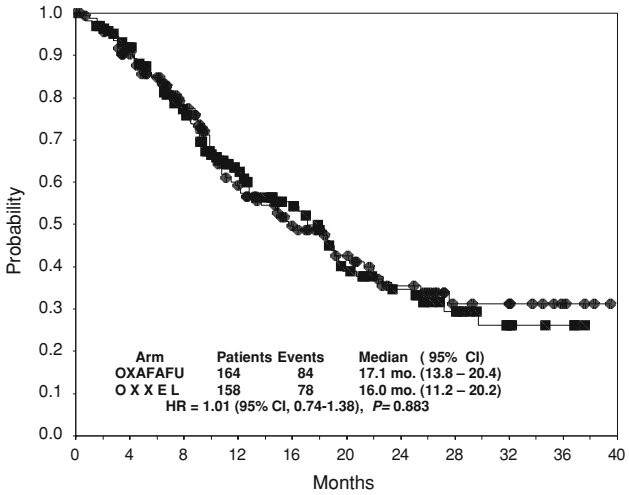

Fig. 2 Estimated overall survival curves according to arms of treatment (OXAFAFU *squares*, OXXEL *circles*)

Discussion

The findings of this study clearly showed that there was no difference in activity between OXAFAFU and OXXEL regimens. Indeed, response rates (33 vs. 34%), and median progression-free survivals (6.5 vs. 6.6 months) were comparable, and the 95% CLs of these results were quite overlapping. However, we should remember that the trial was not powered to demonstrate the non-inferiority of the OXXEL in comparison with the OXAFAFU regimen. Therefore, we cannot exclude that patients treated with the former regimen may have a shorter time to progression than patients treated with the latter.

Moreover, we have to admit that response rate and progression-free survival of patients treated with oxaliplatin plus a fluoropyrimidine in the present trial appear slightly worse than those reported with oxaliplatin and fluorouracil/leucovorin in our previous study (Comella et al. 2005). However, we would underline that the present trial, patients aged ≥70 years represented 36% of the whole series, as opposed to 20% of the previous trial, and we have shown that age was an independent risk factor adversely affecting the response rate in the present study. Moreover, nearly twice more patients (21%) in the present series, as opposed to 11% in the previous trial, had ≥3 disease sites, and the number of involved sites was independently related with a shorter failure-free and progression-free survival in the present study.

As for side effects, we may state that OXXEL was better tolerated than the OXAFAFU regimen. Although severe and febrile neutropenia were infrequent with both regimens, these side effects were significantly reduced with the OXXEL treatment. This safety gain was not counterbalanced by non-hematologic side effects. Indeed, only gastric intolerance was slightly more pronounced with the substitution of oral capecitabine for i.v. fluorouracil/leucovorin.

Regarding quality of life, the diarrhea score derived by the questionnaires was similar in the two arms, while the constipation score showed a slight but significant improvement in patients treated with OXXEL. Of course, we have to remember the limitation of these comparisons, which may have been biased by the mild attrition of patients answering the questionnaire.

To put our results in perspective, we have to mention some randomized trials that also compared the combination of oxaliplatin with either capecitabine or i.v. fluorouracil in metastatic colorectal cancer patients.

In a phase II randomized trial, 118 patients received either the XELOX regimen or oxaliplatin 130 mg/m^2 every 3 weeks combined with fluorouracil 250 mg/m^2 daily as protracted i.v. infusion for 3 weeks. The activity was similar (response rate, 43.5 vs. 48.2%; median progression-free survival, 9 vs. 7 months). However, the XELOX regimen caused less severe diarrhea (8 vs. 13%), and stomatitis (13 vs. 29%) (Martoni et al. 2006).

In the TREE-1 phase II study, 157 patients randomly received: mFOLFOX, bFOL, or XELOX regimen. Response rates were 43, 22, and 35%; median progression-free survival were 8.7, 6.9, and 5.9 months, and median overall survival were 19.2, 17.9, and 17.2 months, respectively. The XELOX regimen produced more severe dehydration (27%) as opposed to mFOLFOX or bFOL regimens, while severe diarrhea had a similar occurrence with all these regimens. The safety advantage of the XELOX regimen was limited to neutropenia, which was much lower (15%) than that reported with mFOLFOX (53%) (Hochster et al. 2006).

A German phase III trial compared in 474 patients the CAPOX regimen with the FUFOX regimen. The former

produced slightly worse response rate (48 vs. 54%, $P = 0.7$), median progression-free survival (7.1 vs. 8.0 months. HR = 1.17, 95% CL, 0.96–1.43, $P = 0.117$), and overall survival (16.8 vs. 18.8 months, HR = 1.12, 95% CL, 0.92–1.38, $P = 0.260$) than the infusional regimen; no safety advantage has been reported for CAPOX, which produced a significantly greater occurrence of grade 2–3 hand-foot syndrome (Porschen et al. 2007).

A Spanish phase IIII trial compared the XELOX regimen with a regimen including weekly infusional fluorouracil plus biweekly oxaliplatin in 348 patients. Although patients treated with XELOX had a lower response rate (37 vs. 46%, $P = 0.539$), and a shorter median time to progression (8.9 vs. 9.5 months, HR = 1.18, 95% CL, 0.9–1.5, $P = 0.153$) and overall survival (18.1 vs. 20.8 months, HR = 1.22, 95% CL, 0.9–1.6, $P = 0.145$), these differences were not significant. In this study, less patients treated with XELOX suffered from severe diarrhea (14% vs. 24%). However, XELOX was associated with more hand-foot syndrome (14 vs. 5%) (Díaz-Rubio et al. 2007).

The NO16966 phase III trial compared the XELOX and FOLFOX4 regimens, before and after the introduction in clinical practice of bevacizumab. A total of 634 patients were treated without bevacizumab: the response rate was 37 vs. 39%, and the median progression-free survival was 7.3 vs. 7.7 months, respectively (HR = 0.96, 97.5% CL, 0.80–1.16). Given the confidence limits of these results, the non-inferiority of the XELOX regimen could be accepted. The XELOX reduced the risk of neutropenia (7vs.43%), but produced more diarrhea (20 vs. 11%) and skin toxicity (6 vs. 1%) than the FOLFOX4 regimen (Cassidy et al. 2007). Subsequently, the addition of bevacizumab or placebo to either FOLFOX4 or XELOX did not increase the overall response rate, which indeed was 47% with bevacizumab and 49% with placebo. Bevacizumab significantly prolonged the progression-free survival (from 8.0 to 9.4 months, HR = 0.83, $P = 0.0023$), but this advantage was significant only for patients treated with XELOX. Excluding the occurrence of hypertension (3.7 vs. 1.2%), severe toxicity was not significantly worsened by the addition of bevacizumab (Salts et al. 2007).

A French phase III trial randomly compared XELOX and FOLFOX6 regimens in 306 metastatic patients. The non-inferiority of the XELOX regimen was proven, because the response rate was 39 vs. 46%, and the 95% upper limit of this difference was below the non-inferiority margin; median progression-free survival was 8.8 vs. 9.3 months (HR = 1.0, 95% CL, 0.82–1.22), and median overall survival was 19.9 vs. 20.5 months (HR = 1.02, 95% CL, 0.81–1.30). XELOX significantly reduced the occurrence of neutropenia (7 vs. 43%), febrile neutropenia (0 vs. 6%), and neuropathy (25 vs. 11%) (Ducreux et al. 2007).

In conclusion, the comparable activity of regimens including oxaliplatin with either oral capecitabine or bolus, short or protracted i.v. infusion of fluorouracil (with or without leucovorin) is consistently supported by all these randomized trials, although it has been formally proven in only two of them (Cassidy et al. 2007; Ducreux et al. 2007). However, a safety advantage for the oral instead of intravenous delivery of fluoropyrimidine has not been clearly established.

In our study, the assessment of quality of life of patients during treatment did not show relevant differences. Other considerations, like patient's preference for an oral therapy, and pharmacoeconomic analyses, could play a role in the choice for the combination regimen. Some investigators have underlined the patient preference for an oral and/or home therapy, provided that it is equally effective to an intravenous regimen (Liu et al. 1997; Twelves et al. 2006); others reported a grater preference for an i.v. regimen, which produced lower acute toxicity (Pfeiffer et al. 2006). Moreover, some studies have shown that capecitabine is associated with reduced costs compared with i.v. fluorouracil/leucovorin in both the adjuvant and palliative setting (Cassidy et al. 2006; Ward et al. 2006), and that the majority of cost savings were due to the reduced administration costs. The additional cost of combining oxaliplatin with capecitabine instead of fluorouracil/leucovorin (Mayer 2007) could be counterbalanced by the lower incidence of some life-threatening adverse events, translating into reduced costs for hospitalization. Moreover, future researches should further elucidate the optimal role of bevacizumab in the management of metastatic colorectal cancer patients, in order to achieve the maximum level of clinical benefit.

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